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A REVIEW ON VALIDATION

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ABSTRACT

Efficient equipment qualification and maintenance are crucial elements in ensuring the quality, safety, and compliance of pharmaceutical manufacturing processes. This review article examines various strategies employed in the industry to enhance efficiency and compliance in equipment qualification and maintenance practices. Firstly, it explores the importance of equipment qualification, encompassing installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ), as essential steps in validating equipment performance. Next, the focus shifts to maintenance strategies, highlighting preventive maintenance, predictive maintenance, and corrective maintenance approaches to minimize downtime and prevent equipment failures. Furthermore, the article delves into the integration of advanced technologies such as predictive analytics, remote monitoring, and condition-based maintenance, which offer opportunities for proactive equipment management and optimization. Additionally, regulatory considerations and compliance requirements set forth by authorities such as the FDA and EMA are discussed, emphasizing the necessity for adherence to current good manufacturing practices (cGMP). Moreover, the review examines the role of risk-based approaches in prioritizing equipment qualification and maintenance activities based on potential impact to product quality and patient safety. Lastly, it discusses emerging trends and future directions in equipment qualification and maintenance, including the adoption of industry 4.0 technologies and the increasing emphasis on sustainability and resource efficiency in pharmaceutical manufacturing operations.

Keywords: FDA, Equipment Qualification, Process Performance Qualification, Pharmaceutical Manufacturing, Maintenance Strategies, Risk-Based Approaches.

I. INTRODUCTION

The equipment qualification in pharmaceutical manufacturing is to ensure that all equipment used in the production process consistently performs according to predefined specifications and regulatory requirements. This process involves validation and documentation whether the equipment is properly installed, operates correctly, and produces the acquired results.

Maintenance of equipment ensures that the medicines produced are of high quality and safe for consumption. Regular maintenance also helps prevent unexpected breakdowns, reducing downtime and ensuring that production runs smoothly.

Efficiency and compliance in pharmaceutical manufacturing can be enhanced through various strategies. These include implementing automated processes to streamline production, conducting regular training for staff to ensure adherence to regulations, and leveraging data analytics to optimize resource allocation and identify areas for improvement. Additionally, fostering a culture of continuous improvement and collaboration across departments can further support efficiency gains while maintaining compliance with industry standards.

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Process validation is done by collection of sufficient data and assessment of data, from the process knowledge gained from product development stage through commercial manufacturing of batches, which establishes scientific evidence that a process is capable of consistently delivering high-quality product.

II. HISTORY

The basic fundamental of Process Validation as first recommended by both Food and Drug Administration (FDA) administrators, Ted Byers and Bud Loftus, in 1979 in United States, to improvement of the pharmaceutical products in quality with low risk, it was offered in main reaction to a number of sterility issues in the bulk parenteral market.

1978: Good Manufacturing Process includes validation.

1987: Guideline for the first validation i.e. on equipment (installation qualification)

2000: A new approach or documented presentation.

2008: Daft guidelines for validating new processes which is implemented on equipment and analytical test validation

2011: A new guideline for process validation issued.

DEFINITION BY REGULATORY AUTHORITIES

1991 European Commission – The Process Validation is "Laws to confirm in accordance with GMP" essentially wants to predictable outcomes meeting its standard specifications.

In 2000: "Documentary confirmation that processes carried out with in its specified limits could be performed efficiently and reproducible to manufacturing of drug products which meetings standard specification as well as quality characteristics."

US Food and Drug Administration (USFDA): "Pharmaceutical Process Validation stands the establishment of documentary proof that delivers a high level of assertion to particular process would continuously manufacture a product that meets pre-determined specification as well as quality attributes."

ICH: "Process Validation is the certifying and documenting the process can repeat and reliably produce an end product (Bulk finish) with essential quality within specified design parameter."

WHO: "Documented form of evidence that any method, process, equipment, approved material, action related to manufacturing process or system actually its intended outcomes."

III. AIM OF PROCESS PERFORMANCE QUALIFICATION

1. The manufacturing process must be validating with individual equipment
2. The aim of Process Performance Qualification activities are to performing a robustness manufacturing activity such a constantly produces medicinal product having minimum inconsistency that meeting its quality standard for pureness, identification and effectiveness.
3. The qualification and validation of equipment, major changes after primary qualification require concurrent validation or verification batch.

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Ultimately process validation will provide reliable products with high reproducibility over time and more confidence on the product which confirm predicated quality, assurance as well as efficiency of the drug product and patient safety.

IV. PURPOSE FOR PROCESS PERFORMANCE QUALIFICATION

Probable reason to execute Process Qualification activities:

Newest Products (Exhibit batches) or current product due to Scale-up and the post approval modifications.

Location variation products.

Updating size of batch.

Updation of any manufacturing formulation like unit formula i.e. composition or components.

Alternate use of vendor (Alternate vendor as for active pharmaceutical ingredients & Excipients).

Updation of specifications or standard test procedure for analysis of drug products.

Change in critical process parameter and critical quality attribute (Measured Response).

Change in building/manufacturing area within the premises.

As required by regulatory bodies or customers.

Atypical trend in product quality parameters as a result of identification during Annual Product Review (APR).

Revalidation as necessary based on annual product quality review that include checking for factors such as deviations, Out of specification, Out of trend, Market complaints.

IMPORTANCE OF PROCESS PERFORMANCE QUALIFICATION

- Assurity on quality of products.
- Time limit ✓ Process optimization
- Quality cost reduction.
- Nominal confusions and bottlenecks.
- Minimum batch failure/error improved efficiency and productivity.
- Reduction in batch rejection.
- Production increases to gives higher output.
- Avoid investment on process optimization.
- Minor comments regarding process related errors.
- Reduction testing of finish product and in process checks.
- Faster and more reliable test run for new plant.
- Easy to scale up in development work.
- Easy to maintain equipment.
- Raising employee awareness related to process activities.
- Faster implementation or automation.
- Government's regulations (Compliance with standard procedure of validation requirements is required to obtain approval for the manufacture and introduction of new products).

V. PRINCIPLE OF PROCEES PERFORMANACE QUALIFICATION

The basic principle of validation can be formulated as follows.

User Requirement Specification (URS) Users' requirement specification (URS), which contains the requirement of the user on behalf of output and quality of product. The specifications used for equipment's, facility, utility otherwise system must be well-defined in URS otherwise in a functioning specifications. This is the important element of quality necessity to be build-up at that phase & whichever GMP risk moderated towards an acceptance levels.

1. Design Qualifications (DQ):

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Establishment by back-ground data and descriptions of equipment application. Select the techniques and also types of equipments, utility, applicable measuring devices with appropriate rationale or justification. Design Qualification (DQ) shall be provided by the vendor. The necessities of that user requirement specifications must be certified for the duration of this design qualifications.

DQ Proposal are:

Description of that purpose and intended use of the equipment.

Descriptions of that proposed environment.

Description for usage of that equipments into the designated atmospheres / process. Primary selectivity of that function as well as performance specification (high-technical, surroundings, protection, security access, compatibility with existing / future systems.

Consultation and documents of contract, accommodation, trainings and supplementary supplier (vendor) facilities.

Verification for Material of Construction (MOC).

Factory acceptance test [FAT] and Site acceptance test [SAT]:

Factory acceptance tests [FAT] and Site acceptance tests [SAT] which containing verification for following with respect to. Design Qualification. FAT might be accompanied by the performance of an SAT subsequent the receipts of equipments at that industrial location.

2. Installation Qualification (IQ):

Establishment of purposes confirmation with all major features for the installation of process equipments as well as auxiliary systems are consistent with the manufacturers authorized specifications and that the equipment supplier's recommendations have been adequately measured.

IQ Proposal are:

Equipment's designed characteristics [that is construction of materials, cleaning condition like easy to clean or hard to clean etc.]

Instalments condition [writing, utilities, functionally etc.]

Calibrations, preventive maintenances, cleaning and washing period.

Security characteristics.

Vendor's documents, design, diagrams and instruction booklet.

Soft copy that is in software documentation.

List of replacement part.

Environment condition such as [Requirement of sanitized areas, temperature, relative humidity etc...]

3. Operational Qualification (OQ):

Established through demonstrative or direct evidence of process measurable limit and actions level that outcomes which is products meets completely specified requirements.

OQ Proposal are:

Process measurable parameters like [Temperature, pressure, time interval, speed of line, operation condition etc...]

Limits of software systems.

Specification and standard test procedure for analysis of raw material.

Standard operating procedure for manufacturing process.

Requirement of handling of the material.

Change control associated with process.

Trainings or self-training through E-learning system.

Short-range stabilities and capabilities [extensive study method as well as control chart.] Possible (i.e. potential) failures mode, action plan and worst case condition.

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At this stage, you can optimize the process using a statistically valid method, such as a selection of experiments design.

4. Performance Qualification (PQ):

After successfully completion of OQ, PQ should be started. An objective proof that the process constantly delivers a products that meeting its pre-determined specified necessities under expected condition.

PQ Proposal are:

Authentic products, all parameter of process and procedures are recognized into the PQ.

All test, via formulating raw-materials, eligible alternatives otherwise simulated products proved that having comparable performance beneath standard operational condition as in worst-case batch proportions. The confirmed process must be justify via frequency of sampling methods.

All the tests must be covered in that operative tentative limit for that proposed process, if documentary confirmation of that development stages assuring to the operating ranges are obtainable.

Repeatable process, long- term process stability.

5. Qualification of Manufacturing

1. Dry powder mixers

- **Type of dr Equipment y powder mixers:**

a) Conical screw mixer.

b) Double cone blender

c) Drum mixer

d) V- cone blender

e) Octagonal blender.

f) Ribbon blender

Applications:

1. Reaction under vacuum or pressure conditions.
2. Dry powder to wet mixing.
3. Drum mixers are used in dye works.
4. Blending drugs, cosmetics, capsule ingredients, pharmaceutical powders, and polymer blends.

2. Try dryer

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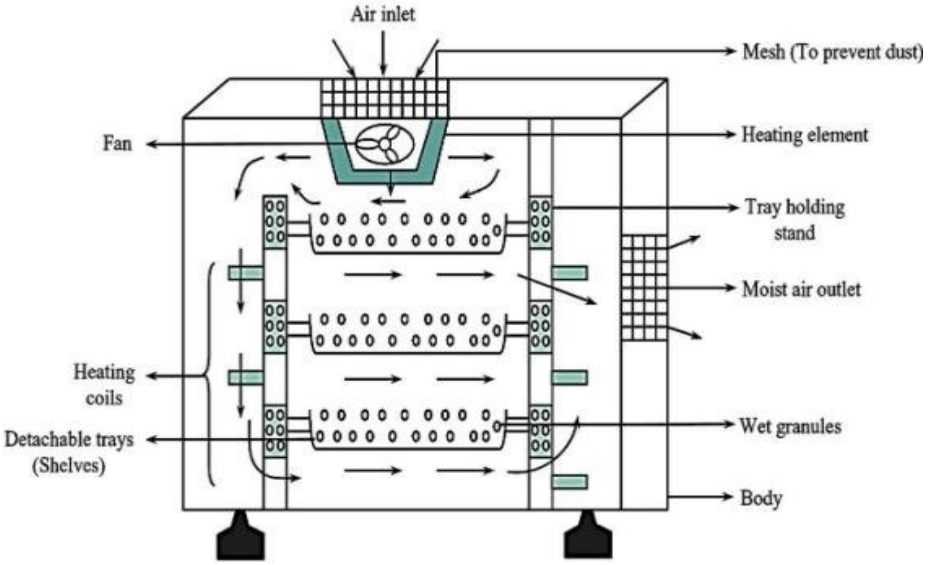

Applications:

- **Industrial application:** Tray dryers can dry and cure coatings, paints, and adhesives in industries like ceramics, plastics, and metalworking.
- **Research and development**: Tray dryers can dry and test samples in research and development laboratories.

3. Tablet compression machine

Applications:

1. This equipment produce tablets for various industries; the most extensive application of rotary tablet presses is pharmaceuticals, medical.
2. Even though the pharmaceutical industry is the biggest recipient of tablet compression machines, there are a variety of high-speed industrial rotary presses.

4. Autoclave

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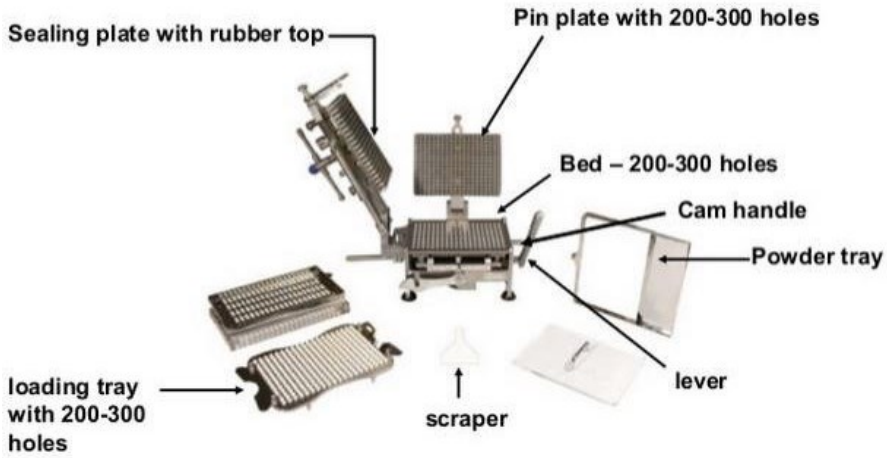
Application:

Sterilizing laboratory equipment: Autoclaves are the most effective and reliable way to sterilize laboratory equipment, media, and glassware.

5. Capsule filling machine



Applications: 1. A common application in the pharmaceutical, food, and chemical I industries.

2. Small, spherical units made from fine powders or granules. Pellets can be used for site-specific drug Delivery.

6. Qualification of Equipment's Used In Laboratories

1. **Friability test apparatus** 1. Switch on the power supply.
2. Set the RPM to 25 and start the machine simultaneously with the stop watch. Count the actual rotations and not the time required for the same.
3. Similarly set the RPM to 100 and note the time required and actual rotations.
4. Apparatus is in proper working condition if,
5. Time required for 25 rotations is 1 min ± 05 sec.
7. Time required for 100 rotations is 4 min ± 20 sec.
8. Record the observation in the calibration record.

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6. Affix a "Calibration Status" label on the instrument.
7. In case of any discrepancy, report the observations to QC manager / QA Manager and notify the defect to Engg.
8. Department Affix an „UNDER MAINTENANCE" label on the instrument.

Frequency: Once in a month and after each maintenance job.

2. Hardness tester

1. Take out the force gauge to be calibrated and hold vertically up.
2. Adjust the zero on the force gauge.
3. Standard Weights are then applied to the hook of force gauge and measure the tension of the spring on the force gauge.
4. When 1 kg of standard weight is applied, scale on the force gauge should also show 1 kg tension produced from the initial point where pointer is adjusted.
5. Adjust the zero on the force gauge again.
6. Follow the same procedure for other weights.
7. The test to be carried out for 1.0 kg, 2.0 kg, 5.0 kg, 10.0 kg, 20.0 kg & 30.0 kg standard weights.

Tolerance: ± 0.25 kg / ± 0.1 kg **Frequency:** Once in 6 months.

3. Disintegration test apparatus

a. Calibration for number of oscillations per minute

1. Take a pre-calibrated stopwatch. Operate the apparatus as per SOP. Start the apparatus and stopwatch simultaneously and count the number of oscillations per minute.
2. Repeat the same for five times and note down the number of oscillations per minute for each time.
3. The oscillations per minute shall be within the limit of 29 to 32 through a distance of 53 to 57 mm throughout the period of operation. Record the observation.

B. Calibration for temperature

1. Switch on apparatus and press key.
2. Turn on the heater by pressing „ON" key.
3. Set the bath temperature by pressing scroll keys.
4. Wait till the temperature of beaker A and beaker B attain the set value.
5. Screen shall show the set temperature of bath and the temperature of beaker A and beaker B.
6. Take a pre-calibrated thermometer and check the temperature of beaker A and beaker B.
7. Record the observation.

C. Timer calibration

- Set the timer for „30 minutes" and start the equipment and stop watch simultaneously. Note down the stop watch reading immediately when the equipment stops and note down the observation.
- Observed time should not deviate by „± 1 min" of set time.

D. Sieve integrity test

- Check the „integrity" of woven stainless steel cloth (Sieve) attached to the base plate of each basket with a pre-calibrated vernier calliper. The sieve has weaven squares of aperture of 1.8 – 2.2 mm and wire diameter of 0.57 to 0.66 mm. Note the observations.
- Affix the „CALIBRATION STATUS" tag duly filled and signed on the equipment after completion of calibration.
- If the instrument is out of calibration then affix „UNDER MAINTENANCE" tag and inform to maintenance department.
- The frequency for calibration of Disintegration Test apparatus shall be after every one month or after every maintenance work.

4. Dissolution test apparatus

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Part 'A'

The instrument shall be calibrated for RPM and Temperature.

For temperature calibration

Measure the temperature of the water bath and of each jar with a calibrated thermometer and compare the result against the digital display on the apparatus.

Acceptance Criteria: 37°C ± 0.5°C

For RPM Calibration

Calibrate the apparatus at 50 and 100 RPM. Compare the RPM shown on the digital display of the apparatus with the RPM measured with a stopwatch or Taco meter.

Acceptable criteria: ± 1 RPM – for 50 RPM ± 2 RPM – for 100 RPM

Part 'B'

Apparatus suitability test disintegrating type

1. Use USP dissolution calibrator disintegrating type 50 mg prednisone tablets.
2. This USP Dissolution Calibrator is provided for the Apparatus Suitability Test in the general chapter of USP 24 or as per the method specified in the documents received along with the respective lot of the tablet.
3. Do not expose the tablets to excessive humidity. Store in dry, cool place.
4. Dissolution Media: Distilled water 500 ml.
5. Using a membrane filter, with stirring for about 5 minutes.
6. Weigh accurately about 10 mg of prednisone reference standard (already dried on 105°C for 3 hour into a 100 ml volumetric flask and dissolve in 5 ml of ethanol. Make up to volume with distilled water.
7. Dilute 10 ml of the solution to 50 ml with distilled water.
8. Conduct the suitability test at conditions mentioned in the certificate of tablets using apparatus I and II.
9. After completion of the dissolution time withdraw filter and aliquot of the solution.
10. Heat the medium with gentle stirring, to about 45° C, immediately filter under vacuum.
11. Discard the first 2 ml of solution and measure the concentration of prednisone at 242 nm against the absorbance of prednisone USP reference standard solution.
12. The apparatus is suitable if each of the individual calculated values for each apparatus at all indicated speeds are within the specified ranges.

Table 1: Basket and basket shaft measurement

S. No	Name of Element	Usp Limit(Mm)
1.	Diameter of shaft	9.4-10.1
2.	Vent hole	2.0
3.	Clear operating	20.2 ±0.1
4.	Shaft base	5.1 ±0.5
5.	Outer diameter of basket base	26.4 ± 3
6.	Inner diameter of basket base	20.2 ±1
7.	Outer length of basket	36.8 ±3
8.	Inner length of basket	27.0 ± 3
9.	Outer diameter of screen	22.2 ±1

Table 2: Paddle and paddle shaft measurement

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S. No.	Name of Element	Usp Limit (Mm)
1.	Longer width of paddle	74.0-75.0
2.	Weight of the paddle	19.0 ±0.5
3.	Lower width of paddle	42.0
4.	Width of paddle	04.0 ±1
5.	Diameter of shaft	9.4-10.1

5. Tap density tester

1. Measure the tapping height (3mm or 14mm) with a ruler
2. Obtain calibrated cylinder (250mL or other volume) from qualified supplier
3. Measure the length of the cylinder.
4. Set the count number and start tapping.
5. Count the tapping number using a stopwatch setting to 1 minute, check the allowed tap number error range as per specific international standard.
6. Weigh the tapping device including the cylinder.

7. Maintenance in pharmaceutical manufacturing

Pharmaceutical manufacturing hinges on rigorous maintenance practices beyond just preventive measures. A comprehensive program incorporates elements like:

1. Risk-based approach: Critical equipment gets prioritized for more frequent checkups to minimize potential risks.
2. Predictive maintenance: Advanced monitoring systems analyze equipment data to predict and address potential failures before they occur.
3. CMMS (Computerized maintenance management systems): Software helps manage work orders, track maintenance history, and streamline the entire process.
4. Highly skilled technicians: Proper training ensures staff can effectively maintain complex machinery and adhere to strict GMP regulations.
5. This multi-faceted approach optimizes equipment performance, safeguards product quality, and keeps production running smoothly.

VI. CONCLUSION

Rigorous equipment qualification and meticulous maintenance are the cornerstones of a robust pharmaceutical manufacturing operation. Qualification ensures equipment meets design specifications and functions as intended. Preventive maintenance programs, with elements like risk assessment, predictive technologies, and skilled technicians, proactively address potential issues before they escalate into costly downtime or product contamination. This integrated approach guarantees consistent production of high-quality pharmaceuticals, safeguarding patient well-being and ensuring compliance with regulatory requirements.

In pharmaceutical industry Process Performance Qualification is the very essential as well as acknowledged Current Good Manufacturing Practices (cGMP) criteria, according to a regulatory requirements. All the critical manufacturing steps should be identified and validated. From manufacturing of drug and its process should be developed and measured to ensure that in process parameters are in place to support process qualification activities and product after execution result of all analytical test must be observed and evaluate with standard specification that product meeting its quality as per regulatory requirements and delivers with patient safety.

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